REMARKS

By way of the above amendments, claims 16 and 17 have been added. Support for the newly added claims can be found at least at page 4-5 last paragraph and page 5, line 16. The newly added claims add no new matter and their entry is respectfully requested.

Rejection Under 35 USC 112

The basis of 112 rejection raised by the Examiner is that the presently pending claims are not entitled to claim priority to PCT application PCT/DE00/00244, filed January 29, 2000, or the US National Phase of this case, US 09/889,802, from which this case depends as a divisional application because the limitation that the dsRNA is 21 nucleotides in length where the "dsRNA consists of two separate non-linked strands" is not supported by the application as filed. The Examiner has stated that the priority date for these limitations is July 2, 2003.

Applicants have added two dependent claims that should be free of this rejection. The dependent claims add the feature that the two separate RNA strands are stabilized by the presence of a chemical linker.

Applicants respectfully traverse this rejection for the previously pending claims based on the following remarks.

The basis of Applicants' claim to priority to PCT/DE00/00244 is that:

1) the priority document discloses and teaches methods of making dsRNA that specifically inhibit the expression of a target gene consisting of strands that are of 15-49 nucleotides where the two strands can be separate or linked;

2) the priority document discloses and teaches a working Example using dsRNA that specifically inhibits the expression of a target gene where the dsRNA consist of two strands that are 21 nucleotides long where the two strands are linked; and

3) the presence of a linker in the working example cannot be viewed as requiring this feature to be added as a further limitation in claims reciting the 21 nucleotide length limitation.

1) PCT/DE00/00244, US 09/889,802, and the instant application disclose methods of making dsRNA of 15-49 nucleotides using separate and linked strands. The texts of PCT/DE00/00244, the US National Phase application US 09/889,802, and the instant divisional application are the same except for the filed claims.

These applications have written description support under 35 U.S.C. § 112 for making dsRNA that specifically inhibits the expression of a target gene by synthetically preparing two separate strands of RNA and then hybridizing them to form a dsRNA that can be 15-49 base pairs. For example, at page 4, lines 1-8 of the application, it is stated that the dsRNA is "preferably 15 to 49 base pairs" and that "Such dsRNA . . . can be produced synthetically" as separate strands.

The Examiner has agreed that "the specification discloses that the dsRNA of the instant invention has 10 to 1,000, preferably 15 to 49, base pairs" (Page 3 of the Office Action) and it is clear from the examples that such molecules were prepared synthetically as two separate RNA strands prior to the two strands being combined (page 17, lines 9-27).

The PCT priority document discloses methods of making dsRNA of 15-49 nucleotides composed of separate strands and linked strands. The application discloses that the dsRNA can be comprised of two separate strands which are synthesized separately. For example, at page 4, line 26 of the application, it is disclosed that "the double-stranded structure is formed by two separate RNA strands or by autocomplementary regions. . ."

The application discloses that the dsRNA, composed of two separate strands, can have an additional chemical linker. For example, in the paragraph spanning pages 4 and 5 of the application, it is disclosed that "to inhibit dissociation in a particularly effective fashion, the cohesion of the complementary region II, which is caused by the nucleotide pairs, can be increased by at least one, preferably two, further chemical linkages."

The above, as well as the Examples, clearly support methods of making inhibitory dsRNA of 15-49 base pairs composed of two separate strands either with or without additional chemical linkage.

2). The PCT application discloses an example within the originally cited claim range.

Applicants provided a working example of the claimed invention. In one Example, at page 17, lines 9-27 of the application, Applicants synthesized two separate RNA strands of 21 nucleotides that contained an additional chemical linkage that were then hybridized to form a dsRNA of 21 nucleotides in length that was then further oxidized via aliphatic linkers and a disulfide bridge to form a dsRNA molecule made from two separate RNA strands that are 21 nucleotides long and which further contained a chemical linker between the two strands that stabilized the dissociation of the two strand. This molecule was shown to be effective at inhibiting the expression of a target gene in a mammalian cell.

3). Applicants are entitled to use a value presented in an example as a replacement for a previously recited range that includes this value.

Applicants used the working example of a dsRNA 21 nucleotides in length as a basis to amend the originally filed claims to replace the length range disclosed and claimed in the application, namely the original length range of 15 to 49 with or without a linker was amended to claim the internal value of 21 nucleotides which is exemplified in data provided in the application. The Examiner rejected this amendment as new matter stating that Example teaches the use of a dsRNA made of strands 21 nucleotides in length with a linker and a linker needs to be present in any claim that relies on this Example as a basis for amendment. Applicants disagree.

The presence of the chemical linkage in the 21 nucleotide example does not eliminate from the scope of conception of the originally filed invention for "linked and non-linked dsRNA", it is simply an exemplification of a single embodiment. Applicants have used one of the features of this embodiment, strand length of 21 nucleotides, to provide support for the amended length limitation of 21 nucleotides. There is nothing in the Example that suggest that the only way the Applicants viewed that such agents could be made and used were as chemically

linked molecules (as suggested by the Examiner) because it is clear that the inventors contemplated that additional chemical linkages was an optional element.

In the present pending claims, the pertinent feature of length, 21 nucleotides, is distinct from and separate from the other disclosed limitation, such as linked versus non-linked. In the Office Action, the Examiner simply states that the linked dsRNA of 21 nucleotides in length is considered to be a different molecule than the instantly claimed dsRNA specifically consisting of two separate strands. However, as stated in Wertheim "The burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not *in ipsis verbis* is insufficient" **In re Wertheim at page 265, column 1, see also In re Lukach 442 F.2d 968.** The Examiner has not met this burden here and the case law precedent supports Applicants' position.

The Fire and Mello patent of record exemplifies the use of using long dsRNA, with C. elegans, an invertebrate organism without an interferon response. Table 1 of Fire provides the agents actually used and shown to work: 17 agents, the shortest of which is 299 nucleotides. However, the Patent contains claims and prophetic descriptions of the use of dsRNA that is longer than 25 nucleotides at length. However, the Fire Patent was published after the filing of the priority DE applications and was not known by the present inventors. What was known to Applicants was the Fire Nature 391:806-811 (1998) which showed only the use of long (>299nt) dsRNA in C. elegans. Neither the Fire Patent nor publication identified the problem solved by the present invention, a kinase or other cellular response to long dsRNA found in mammalian cells.

Applicants noted at page 3 of the application that unlike Fire that taught the use of long dsRNA, by using shorter dsRNA you would not induce "dsRNA-dependent kinase or the 2-5A system, in mammalian or human cells" which leads to a "disappearance of the interference effect mediated by the dsRNA." This observation, which formed the basis of the claimed invention, was made prior to the publication of the Elbashir reference cited by the Examiner as showing the importance of length in avoiding an interferon response which leads to cell death and non-specific RNA degradation.

The presently pending claim length, 21 nucleotides, solves the same problem as the original range 15-49 nucleotides, namely the drop in inhibitory effect of dsRNA in mammalian cells can be reduced using shorter dsRNA. The Examiner has cited an "after the invention" reference as showing that less than 30 nucleotides is preferred. Applicants' invention teaches that the inhibition of the RNAi effect can be reduced by decreasing the size of the dsRNA used and that this decrease in inhibiting the RNAi effect appears at less than 49 nucleotides and continues to 15 nucleotides. It is not surprising that the later published Elbashir reference cited by the Examiner supports this and stresses that even less than 30 is better, not a different invention, same problem solved.

At page 4 of the Office Action, the Examiner has incorrectly stated that "As is well known in the art and as first disclosed by Elbashir . . . the discovery of 21 and 22 nucleotide duplexes are capable of specific gene inhibition . . .". However what is clear is that the PCT priority applications which Applicants assert provides support for the presently pending claims, does provide a working example of a dsRNA that is 21 nucleotides long. This 21 nucleotide dsRNA Example was included in Applicants' filing prior to the publication of Elbashir. Clearly, Elbashir did not predate Applicants in finding gene specific inhibition using a dsRNA 21 nucleotides in length.

As such, the rejection may be properly withdrawn.

Rejection under 35 USC 102

At page 5 of the Office Action, the Examiner has rejected the claims under 35 USC 102 as anticipated by Elbashir or Tuschl. The Examiner's rejections is based on the position that the present claims are not supported by the priority documents and are only afforded a priority date of July 2, 2003. As such, the Examiner has cited two references that were published after the priority applications but before the date of the instant application as prior art which anticipates the claimed invention.

As discussed extensively above, the presently pending claims are supported by the PCT priority application and therefore the effective filing date for these claims is January 29, 2000.

The references cited by the Examiner are not available as prior art since they were published after January 29, 2000 (Elbashir (Nature 2001) and Tuschl (WO 02/44321)).

Accordingly, all of the prior art rejections may be properly withdrawn.

SUMMARY

Applicants have added two dependent claims and have further presented arguments to rebut the Examiner's rejections. It is believed that the rejections have been addressed and that the application is in condition for allowance. It is requested that the Examiner contact Applicants' undersigned representative if the Examiner believes that a telephonic interview would expedite this case.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States.

Please apply any necessary charges, including the one month extension fee, and any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 14174-104US5.

Respectfully submitted,

Date: 8/08/07

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